

TOBACCO PRODUCT ABUSE LIABILITY: A GOLDBLOCKS PARADOX

Presented by

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DISCLAIMER



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INTRODUCTIONS

- **Lynn Hull, Ph.D.** – Center for Tobacco Products (CTP), Office of Science (OS), Deputy Director, Division of Individual Health Science (DIHS)
- **Megan Schroeder, Ph.D.** – CTP, OS, DIHS, Behavioral and Clinical Pharmacology Branch Chief



- Abuse Liability & Public Health Standard
- Abuse Liability Outcomes
- Product Characteristics that Influence Abuse Liability
- Study Design Considerations



- The ability of a product to promote continued use and the development of addiction and dependence.
 - Product substitutability
 - Results in patterns of continued use
 - Reduces the likelihood of product quitting



EMPLOYING A PUBLIC HEALTH STANDARD

- Congress created **a new regulatory standard** in the Tobacco Control Act—one that is geared toward reducing the public health toll that tobacco use poses to all Americans, not just individual users
- FDA regulates tobacco products based on a **public health standard** that considers the risks and benefits of the tobacco product on the population as a whole



- “People smoke for nicotine, but they die from the tar.” – Michael Russell
- Informs the likelihood that addicted users of one nicotine product would switch (e.g., dual use, exclusive use) to another.
- Informs the likelihood that new users of a product will progress to regular use.
- If a new product has a high abuse liability, current addicted tobacco users interested in quitting may find it to be an adequate substitute for the product they are currently using. On the other hand, low abuse liability makes it less likely that new users will become addicted.

THE GOLDBLOCKS PARADOX





ABUSE LIABILITY OUTCOMES

ABUSE LIABILITY OUTCOMES

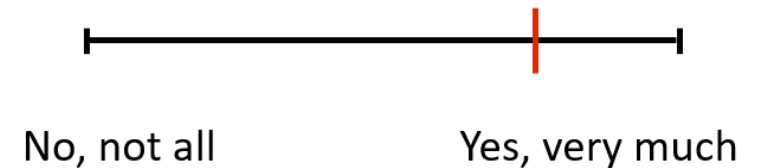
- No one outcome can fully inform abuse liability
 - “Totality of evidence”
- **Behavioral Pharmacology:** study of effects of drugs on user behavior
 - e.g., frequency of use, puff topography, subjective effects
- **Clinical Pharmacology:** study of drugs in humans
 - Pharmacokinetics, pharmacodynamics
 - e.g., biomarkers of exposure, physiological responses



- Self-reported assessments measure drug reinforcement, dependence
 - Self-reported subjective effects
 - Positive: “liking,” “satisfaction,” “pleasure,” “taste,” “strength,” and “stimulation”
 - Negative: “dislike” and “unpleasant”
 - Validated questionnaires
 - Fagerström Test for Nicotine Dependence (FTND)
 - Nicotine Dependence Syndrome Scale (NDSS)
 - Wisconsin Inventory of Smoking Dependence Motives (WISDM)

Likert Scale

Do you like the drug effect?



Use behavior:

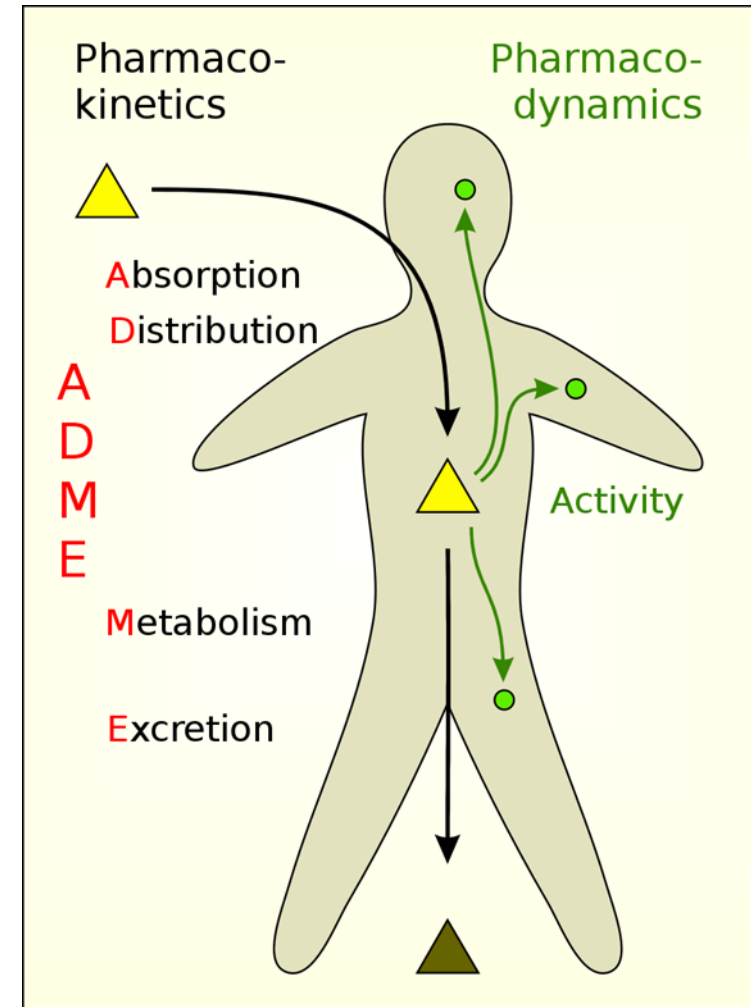
- Puff topography (inhaled products): quantitative measure of puffing behaviors
- Cigarettes per day
- Deposition time (smokeless tobacco)
- Inhalation behavior (cigars)
- Polytobacco use/switching



Image source: Robinson et al., 2015

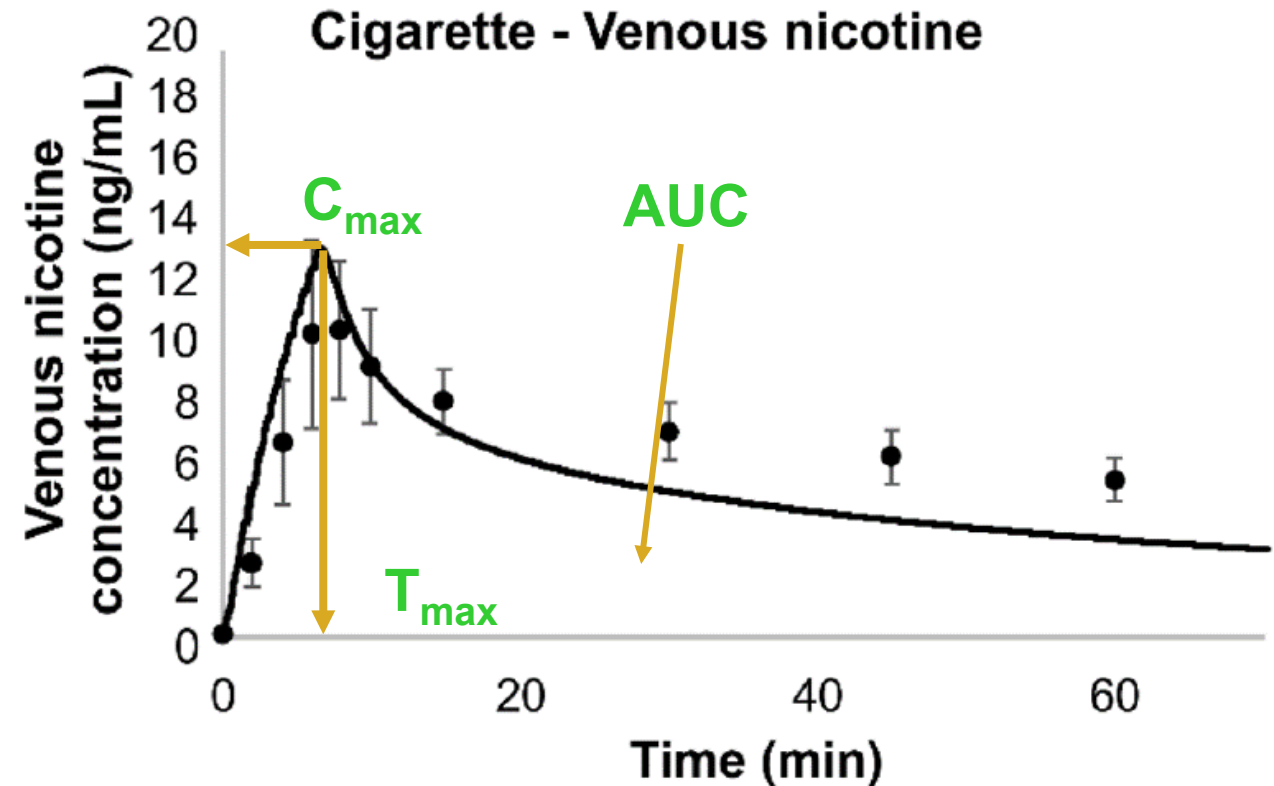
CLINICAL PHARMACOLOGY MEASURES

- Pharmacokinetics (PK): how the body affects a specific drug
 - Absorption
 - Distribution
 - Metabolism
 - Excretion
- Pharmacodynamics (PD): a drug's pharmacological effect on the body
 - Objective (heart rate)
 - Subjective (pleasurable)



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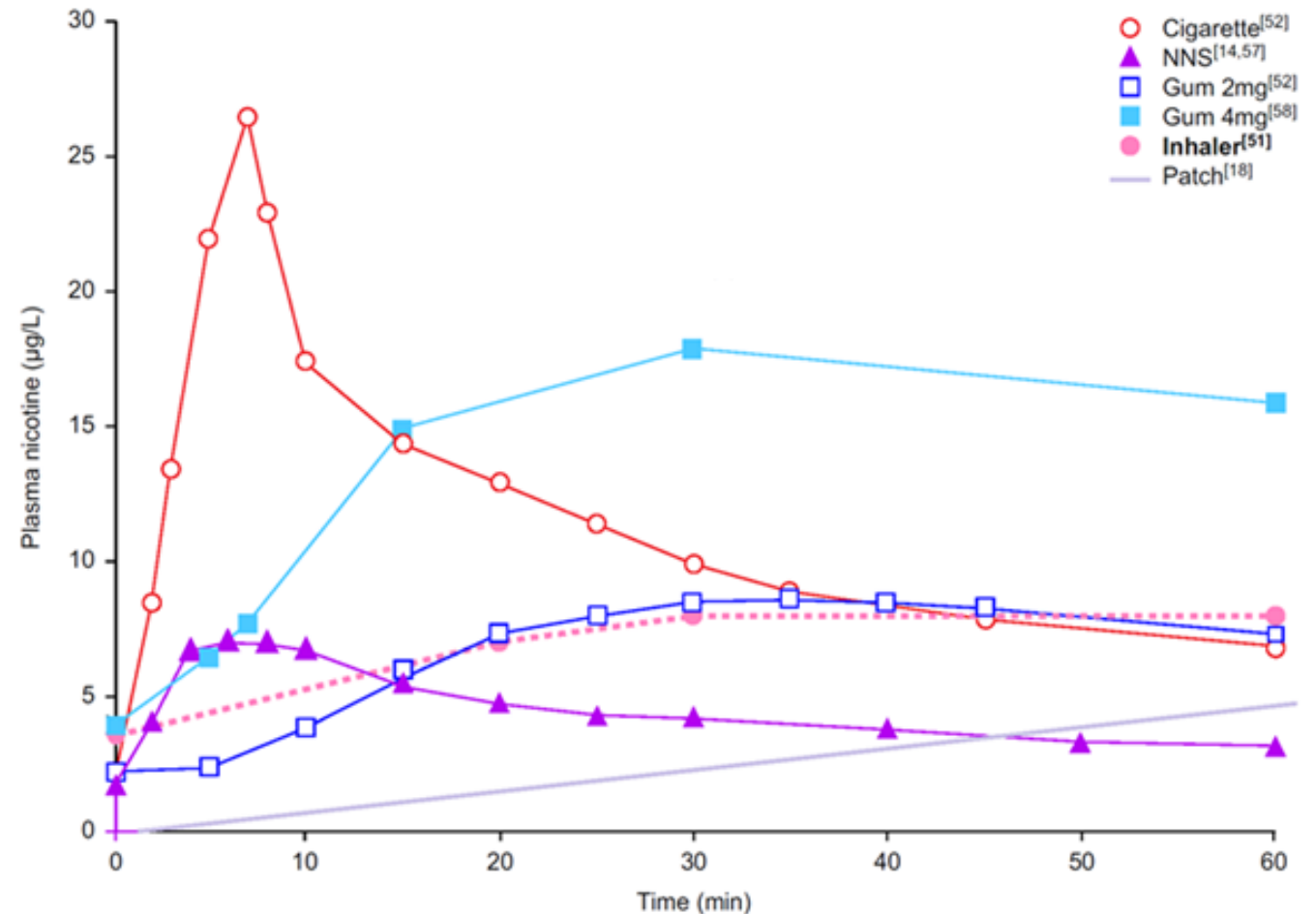
- Nicotine Pharmacokinetics (PK):
 - C_{max} – maximum drug concentration
 - T_{max} – time to maximum drug concentration
 - **AUC** – area under the concentration vs. time curve



Rostami et al 2022

CLINICAL PHARMACOLOGY OUTCOMES

- Nicotine pharmacokinetics of nicotine-containing products varies
- Tobacco product abuse liability “continuum”: comparison to products with known abuse potential



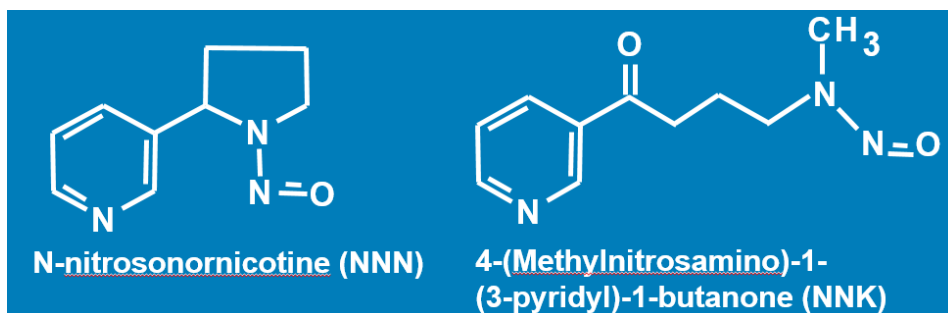
Adapted from Schneider et al., 2001

- Biomarkers of exposure (BOE)

- Biological samples

- Plasma
- Urine
- Saliva
- Breath

- Nicotine
- Cotinine
- Total nicotine equivalents (TNE; nicotine, cotinine, and other nicotine metabolites)
- Carbon Monoxide (CO)
- Harmful and potentially harmful constituents (HPHCs) or their metabolites (e.g., N-Nitrosornicotine [NNN], Benzo[a]pyrene [BAP]).



<https://www.fda.gov/tobacco-products/products-ingredients-components/harmful-and-potentially-harmful-constituents-hphcs>



PRODUCT CHARACTERISTICS THAT INFLUENCE ABUSE LIABILITY

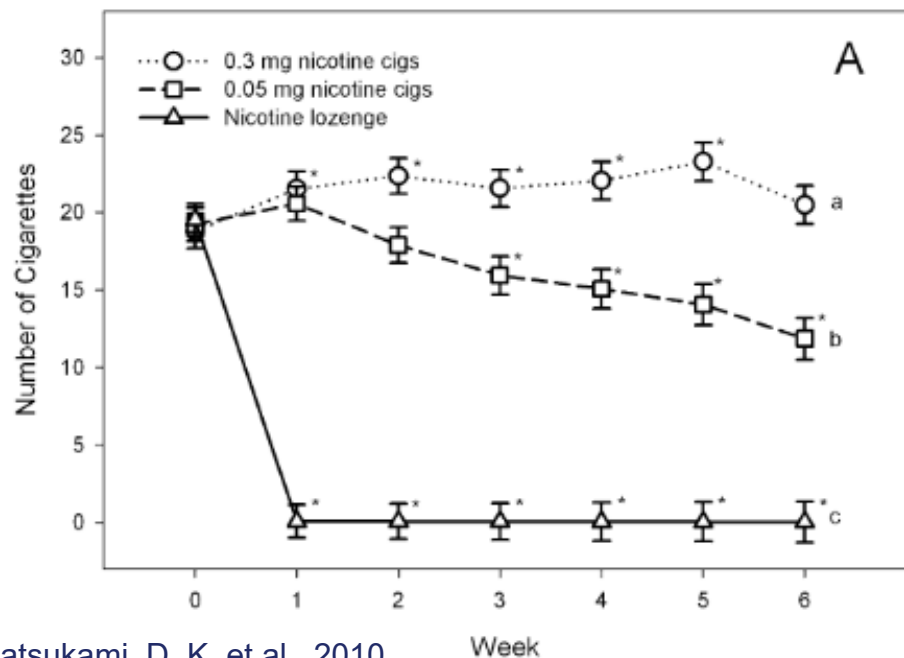
NICOTINE CONTENT/YIELD



Generally, as nicotine content/yield increases, abuse liability increases

Decreases in nicotine content reduces cigarettes per day (CPD)

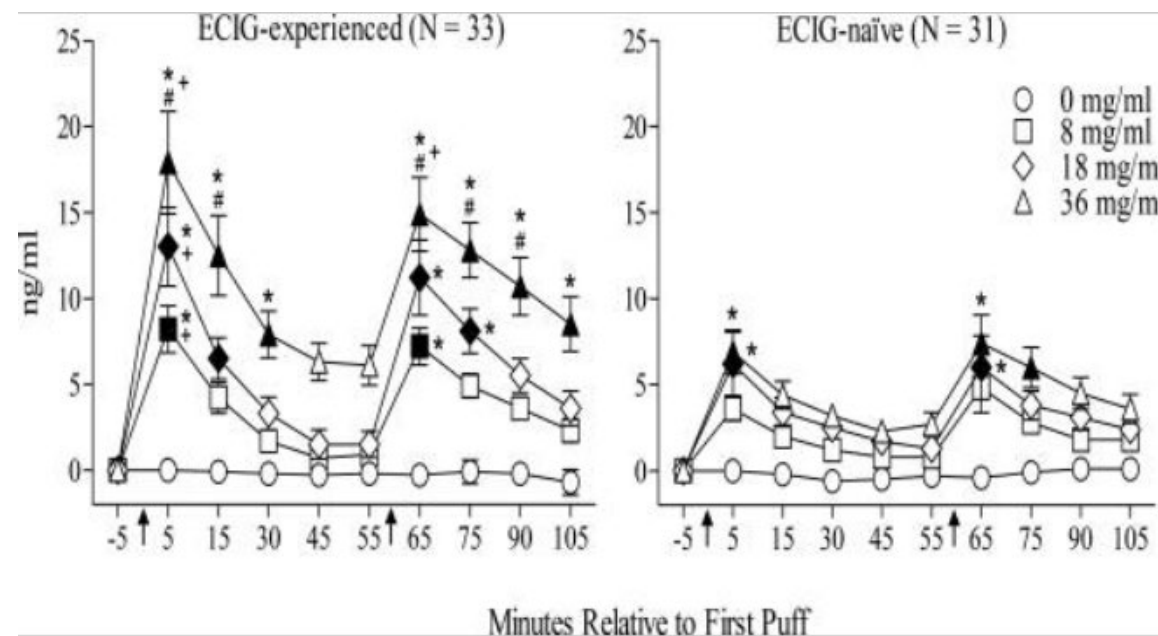
Cigarettes



Hatsukami, D. K. et al., 2010

Increases in e-liquid nicotine content increase nicotine exposure

Electronic Nicotine Delivery Systems (ENDS)



Hiler M, et al., 2017

CIGARETTE VENTILATION HOLES

Ventilated, non-vent blocked cigarettes may have greater abuse liability than non-ventilated cigarettes.¹

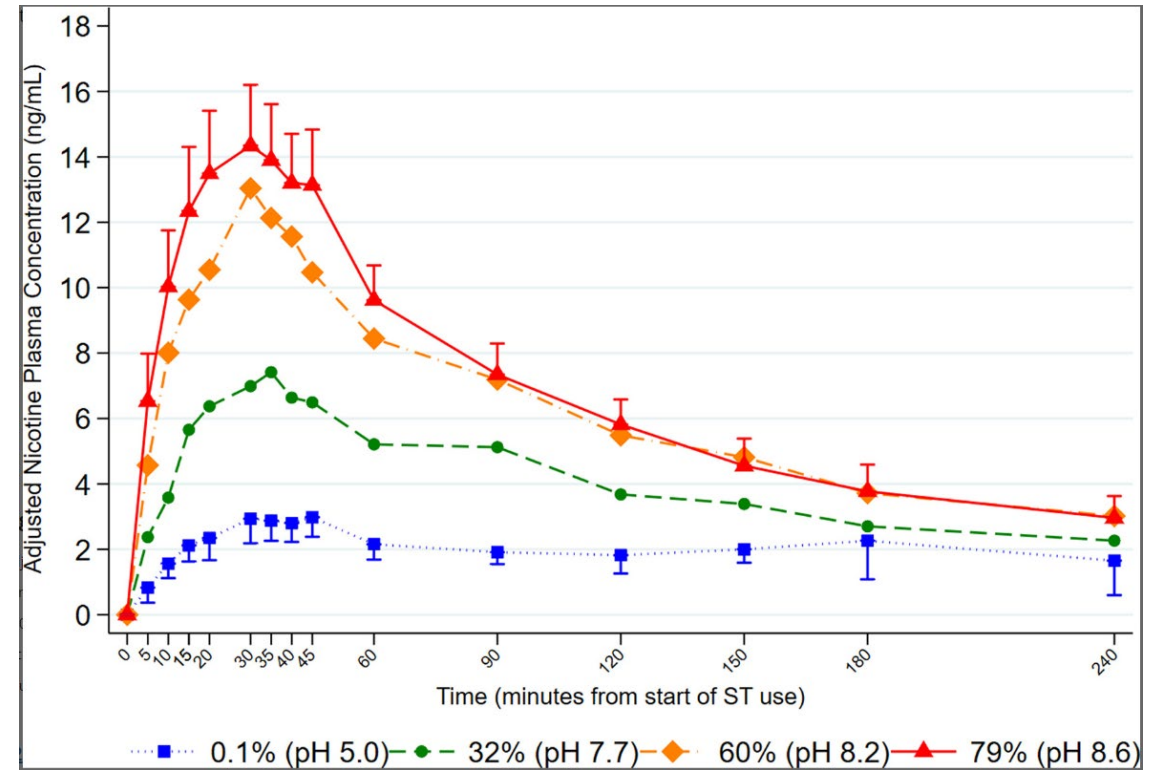
- Increasing cigarette ventilation allows air to mix with smoke before inhalation, lowering the smoke temperature and decreasing harshness.²
- Reducing cigarette ventilation may result in increased delivery of HPHCs, including nicotine.³



E.g., 1: Stein et al., 2018; 2: Kozlowski & O'Connor, 2002; 3: Caraway et al., 2017

Smokeless tobacco pH affects abuse liability.¹

- As pH increases (increased free nicotine content), nicotine exposure increases.
- Higher free nicotine results in larger, more rapid increases in plasma nicotine.^{2,4}
 - Associated with increased use and greater signs of dependence.³



Whilhelm et al., 2022

1: Fant RV et al., 1999; 2: Pickworth WB et al., 2014; 3: Tomar et al., 1995; 4: Whilhelm et al., 2022

Smokeless tobacco pH affects abuse liability.

- Low free nicotine may increase initiation.¹
- Survey studies and industry documents suggests that “starter” products with low free nicotine are marketed to inexperienced users ^{1,2}
- Consumers who begin with starter products likely to progress to products with higher free nicotine



1: Tomar et al., 1995; 2: Connolly GN et al.,1995

CHARACTERIZING FLAVORS

Non-tobacco flavors in ENDS may increase abuse liability.

- ENDS flavors are associated with product initiation and progression to regular use, particularly among youth.¹

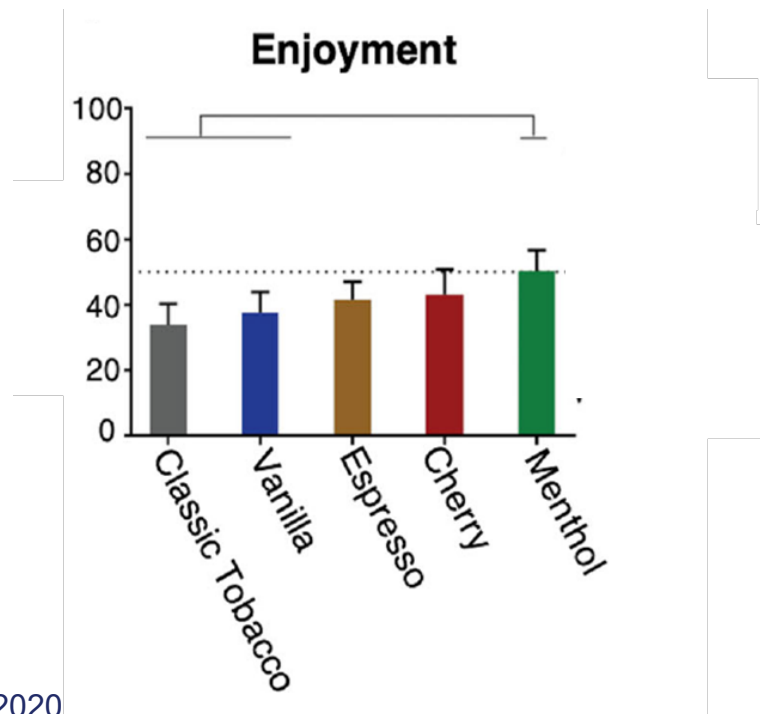


1: Villanti et al., 2019

Image source: CDC

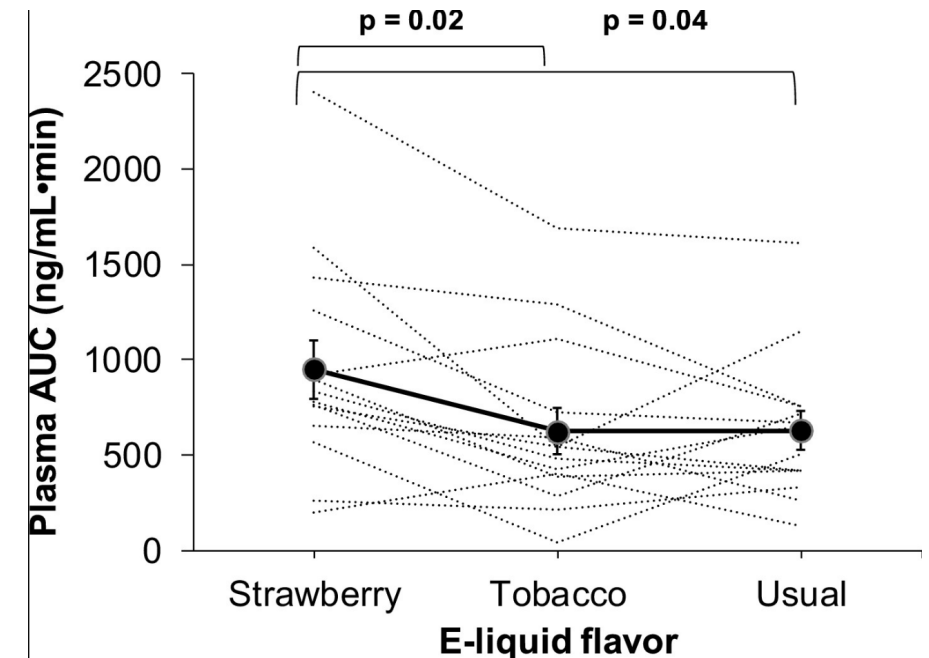
CHARACTERIZING FLAVORS

Flavors may mask the harshness of nicotine, making the products more enjoyable.¹



1: Voos et al., 2020

Flavors may increase use behavior¹ and nicotine exposure compared to tobacco-flavored e-liquid.²



2: St.Helen et al., 2017

CHARACTERIZING FLAVORS - MENTHOL

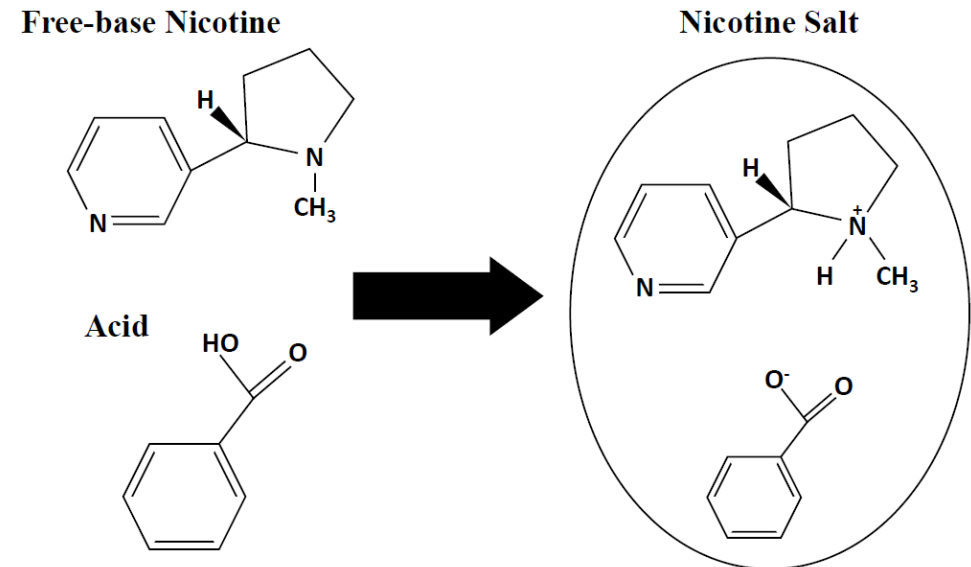
- Menthol CC smokers may prefer menthol-flavored ENDS over tobacco-flavored ENDS.¹
- Menthol cigarettes promote dependence in youth² and decrease cigarette cessation, particularly in Black Americans.³



1: Denlinger-Apte, R. L. et al., 2021; 2: Nonnemaker et al., 2013; 3: Mills et al., 2020

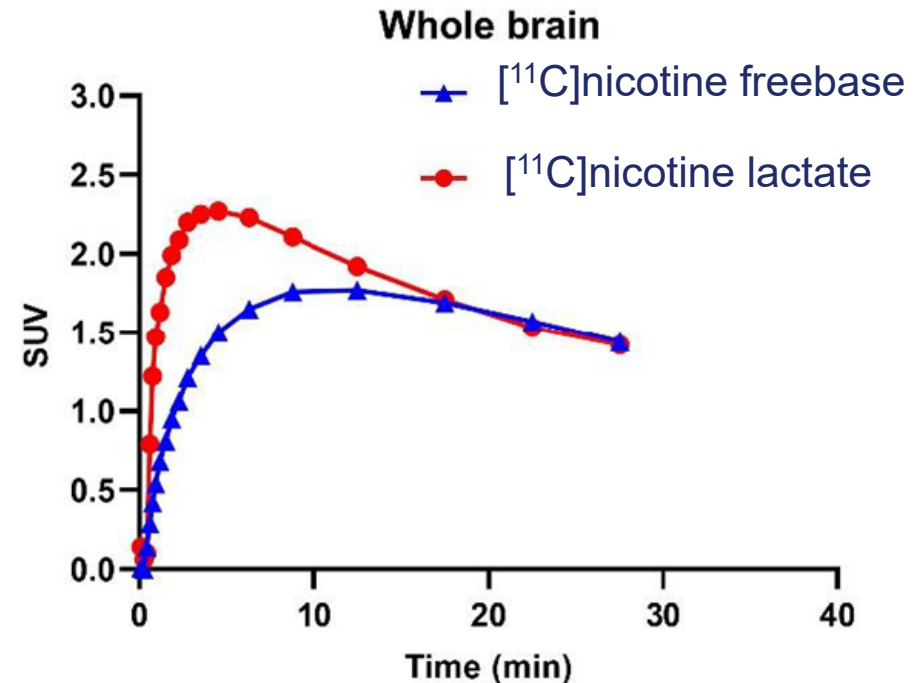
E-liquid nicotine salt formulations may increase abuse liability.

- Freebase Nicotine (basic)
- Nicotine salts are complexes of nicotine and volatile organic acids (e.g., benzoate and lactate)
- Acid + Nicotine = nicotine salt



NICOTINE FORMULATION

- Nicotine salts have a lower pH (e.g., lower than 7), and may decrease throat irritation with inhalation, and could alter nicotine exposure.¹
- Nicotine salts may be associated with faster nicotine uptake.²
 - Nicotine lactate was taken up in the lungs and brain much faster and reached deeper areas of the lungs than the free-base nicotine.



1: Goniewicz et al., 2019; 2: O'Connell et al., 2019

Wall et al., 2022



STUDY DESIGN CONSIDERATIONS

STUDY DESIGN CONSIDERATIONS

- Abuse liability assessments may include:
 - use topography or other actual use measure
 - pharmacokinetics and pharmacodynamics (e.g., subjective effects)
- The “standard abuse liability study” may not be sufficient for some tobacco products.
 - Additional considerations for tobacco products



Additional considerations:

- Appropriate comparison product
 - Comparison to one or more tobacco products to understand how a product compares to other relevant categories of tobacco products
- Ways consumers actually use the product vs. how manufacturers intend the product to be used
- Study duration
- Population
- Bridging
 - E.g., using the results of a study conducted on a different product to inform FDA about the new product
 - Need to justify the bridging, show how key similarities between the products demonstrate the results of the study apply to the new tobacco product.



IN SUMMARY

- Abuse liability of a product can promote continued use and lead to addiction and dependence.
- FDA regulates tobacco products based on a **public health standard** that considers the risks and benefits of the tobacco product on the population as a whole
- Goldilocks paradox:
 - High abuse liability → contribute to continued use/sustain addiction
 - Low abuse liability → may be an inadequate substitute product for users looking to quit

SUMMARY

- Product characteristics can influence abuse liability
 - E.g., nicotine content/yield and nicotine formulation, smokeless tobacco pH
- Study design for abuse liability in tobacco products has unique considerations
 - E.g., appropriate comparison products, how consumers actually use the products





Thank You!

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